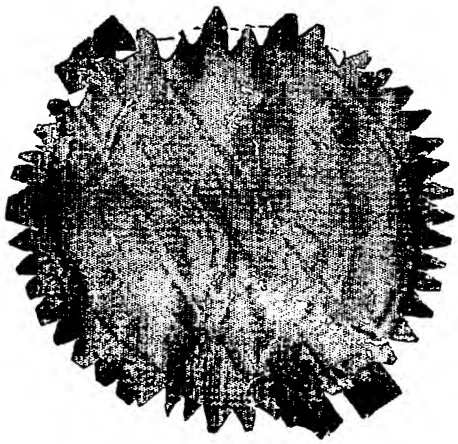
IBOA/02959

सत्यमेव जयते

INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.* ***1145/Del/2003*** *dated* ***12th September 2003.***



Witness my hand this 13th day of January 2005.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR THE PREPRATION OF 3-CYCLOPROPYLMETHOXY-4-DIFLUOROMETHOXY BENZOIC ACID"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. PROSENJIT BOSE

b. YOGINDER PAL SACHDEVA

c. RAMENDRA SINGH RATHORE

d. YATENDRA KUMAR

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

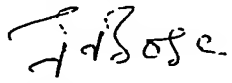
6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

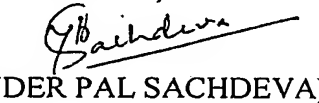
8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

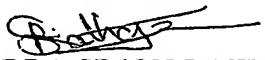
9. Following declaration was given by the inventors or applicants in the convention country:
We, PROSENJIT BOSE, YOGINDER PAL SACHDEVA, RAMENDRA SINGH RATHORE, YATENDRA KUMAR of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. 

(PROSENJIT BOSE)

b. 

(YOGINDER PAL SACHDEVA)

c. 

(RAMENDRA SINGH RATHORE)

d. 

(YATENDRA KUMAR)

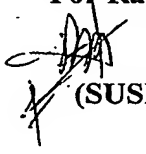
10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
   a. Complete Specification (3 copies)
   b. Drawings (3 copies)
   c. Priority document(s)
   d. Statement and Undertaking on FORM – 3
   e. Power of Authority (Not required)
   f. Fee Rs.**3,000/-** (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this **12TH** day of **September, 2003.**

For Ranbaxy Laboratories Limited



(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

PROCESS FOR THE PREPARATION OF 3-CYCLOPROPYLMETHOXY-4-DIFLUROMETHOXY BENZOIC ACID

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

An industrially advantageous process for the preparation of 3-cyclopropylmethoxy-4-difluromethoxy benzoic acid, a key intermediate for the synthesis of roflumilast, is provided.

3-cyclopropylmethoxy-4-difluromethoxy benzoic acid is an useful intermediate for roflumilast. known from US 5,712,298. Roflumilast is an effective phosphodiesterase-4-inhibitor (PDE4-inhibitor), which can be used in the treatment of asthma, inflammation, bronchitis, allergy, osteoporosis, dermatoses and disorders related to immune system, heart and kidney.

US 5,712,298 discloses the preparation of 3-cyclopropylmethoxy-4-difluromethoxy benzoic acid comprising reacting 4-hydroxy-3-cyclopropylmethoxybenzaldehyde with dichlorofluromethane followed by oxidation. US 6,712,274 discloses a synthetic scheme for the preparation of 3-cyclopropylmethoxy-4-difluromethoxy benzoic acid comprising reacting dihydroxybenzaldehyde with tertiarybutyl difluorochloroacetate in the presence of lithium carbonate and reacting the obtained 4-difluoromethoxy-3-hydroxy benzaldehyde with cyclopropylmethyl bromide in the presence of potassium carbonate followed by oxidation to yield 3-cyclopropylmethoxy-4-difluromethoxy benzoic acid.

In one aspect there is provided a process for the preparation of 3-cyclopropylmethoxy-4-difluromethoxy benzoic acid of formula I, as shown in the accompanied drawings, comprising reacting the compound of formula II as shown in the accompanied drawings wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl with difluoro-methylating agent in the presence of a base followed by desterification of obtained compound of formula III, as shown in the accompanied drawings wherein R is as defined above, to obtain the compound formula I.

In a further aspect, a process for the preparation of 3-cyclopropylmethoxy-4-hydroxy benzoate of formula II is provided comprising reacting 3,4-dihydroxy benzoate of formula IV, as shown in the accompanied drawings, wherein R is as defined above with cyclopropylmethyl derivative of formula V, as shown in the accompanied drawings wherein X is a leaving group, in the presence of a base.

In yet another aspect, new compounds of formula II and III, which are useful intermediates, are provided.

The compound of formula I may be converted to 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluromethoxy)benzamide i.e roflumilast of formula VI, as shown in the accompanied drawings, by methods known in the literature for amide formation, including those reported for roflumilast such as US 5,712,298 and US 6,712,274, which are incorporated herein by reference.

Examples of alkyl group include methyl, ethyl, propyl, isopropyl, butyl, secondary butyl and tertiary butyl. Examples of alkenyl group include vinyl, allyl, isopropenyl, pentenyl and hexenyl.The substituted phenyl includes phenyl substituted by 1-3 substituents, which are independently bromine, chlorine, fluorine, C_1-C_4 alkyl, C_1-C_4 alkoxy, and nitro groups. Examples of alkoxy group include methoxy, ethoxy, propoxy, isopropoxy and butoxy. The substituted benzyl includes p-nitro benzyl, p-methoxy benzyl, o-nitro benzyl, p-bromo benzyl or 2,4,6-trimethyl benzyl groups.

The difluoromethylating agent used for preparing 3-cyclopropylmethoxy-4-difluromethoxy benzoic acid of formula I, include difluorochloromethane (freon-22®), alkyl difluorochloroacetate such as methyl difluorochloroacetate, ethyl difluorochloro acetate and tertiarybutyl difluorochloroacetate.

The base, which may be used for preparing 3-cyclopropylmethoxy-4-difluromethoxy benzoic acid of formula I, include organic and inorganic bases. Examples of organic base include trimethylamine. triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, DBU (1,8-diazabicyclo- [5.4.0]-undec-7-ene), DBN (1,5-diazabicyclo-[4.3.0]-non-5-ene), 4-dimethylamino pyridine and mixtures thereof. Examples of inorganic base include alkali metal carbonate, bicarbonate, hydroxide and mixtures thereof. Examples of alkali metal carbonate include lithium carbonate, sodium carbonate and potassium carbonate. Examples of alkali metal bicarbonate include sodium bicarbonate and potassium bicarbonate. Examples of alkali metal hydroxide include sodium hydroxide and potassium hydroxide.

The reaction of compound of formula II with difluoromethylating agent may, if desired, be carried out in the presence of phase transfer catalyst. Phase transfer catalyst used, are not limited though, they are quaternary ammonium salts, or quaternary phosphonium salts generally. Examples of quaternary ammonium salts include tetramethyl ammonium iodide, tetrabutyl ammonium iodide, benzyltributyl ammonium bromide, 1-methylpyridinium iodide, tetramethyl-2-butylammonium chloride, trimethylcyclopropylammonium chloride, tetrabutylammonium bromide

and t-butylethyldimethylammonium bromide. Examples of quaternary phosphonium salts include tributylmethylphosphonium iodide, triethylmethylphosphonium iodide, methyltriphenoxyphosphonium iodide, tetrabutyl phosphonium bromide, benzyltriphenyl phosphonium bromide, and tetraphenyl phosphonium chloride.

The reaction of compound of formula II with difluoromethylating agent may carried out in the presence of a suitable solvent. Suitable solvents are inert organic solvents that do not change under the reaction conditions. Examples of such solvents include alkyl ethers such as diethylether, diisopropylether and dimethoxyethane; nitriles such as acetonitrile and benzonitrile; alcohols such as methanol, ethanol, isopropanol and butanol; ketones such as acetone and methyl isobutyl ketone; chlorinated hydrocarbons such as methylene chloride, ethylene dichloride and carbon tetrachloride; esters such as ethylacetate and isopropylacetate; hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane, heptane and octane; dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide; cyclic ethers such as dioxane and tetrahydrofuran, and mixtures thereof.

The temperature at which the reaction may be carried out is not critical. For example the reaction may be performed at temperatures of from about 20°C to about 120°C. The reaction may be performed at temperatures of from about 25°C to 50°C in some particular embodiments.

The compound of formula III is converted to the compound of formula I by conventional methods including hydrolysis or hydrogenation, in case R is a benzylic group.

Examples of leaving group X, in the compound of formula V, include chlorine, bromine, iodine, sulphate and tosylate.

The base, phase transfer catalyst and solvent, which may be used for preparing 3-cyclopropylmethoxy-4-hydroxy benzoate of formula II from compound of formula IV can be the same as those which can be used in reaction of compound of formula II with difluoromethylating agent.

The temperature at which the reaction may be carried out is not critical. For example the reaction may be performed at temperatures of from about 20°C to about 120°C. The reaction may be performed at temperatures of from about 25°C to 50°C in some particular embodiments.
In general, roflumilast of formula VI is prepared by reacting an activated derivative of the acid of formula I, such as acid halide or a reactive ester, with 4-amino-3,5-dichloro pyridine. For example, roflumilast can be prepared by reacting the corresponding acid chloride of the compound of formula I with 4-amino-3,5-dichloro pyridine in the presence of sodium hydride in tetrahydrofuran.

In the following section embodiments are described by way of examples to illustrate the process of invention. However, these are not intended in any way to limit the scope of the present invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

Example-1

Preparation of 3-Cyclopropylmethoxy-4-hydroxy methyl benzoate

3,4-Dihydroxy methyl benzoate (50 g) was stirred with cyclopropylmethyl bromide (50.2 g) and potassium carbonate (82.1 g) in acetone (350 ml) for 18 hours at 40°C. The reaction mixture was filtered over a hyflobed followed by concentration of organic layer.

The crude product was purified over a silica gel column (on eluting with 5 % ethyl acetate in hexane) to afford pure title product.
Yield: 16 g.
HPLC Purity: 99.5%

Example-2

Preparation of 3-Cyclopropylmethoxy-4-difluoromethoxy benzoic acid

The product obtained from example-1 (10 g) was subjected to difluoromethylation using diflurochloromethane, 35 % w/w sodium hydroxide aqueous solution (50 ml), tetrabutyl ammonium bromide (5.9 g) in toluene (100 ml) as solvent at 20 to 35° C. The resulted product, 3-

cyclopropylmethoxy-4-difluoromethoxy methyl benzoate was hydrolysed insitu by adding 50 ml water and heating the reaction mixture to 50 to 55°C. pH of reaction mixture was adjusted to 3-4 by adding concentrated hydrochloric acid at 20 to 30°C followed by extraction with ethyl acetate (48 ml) .The solvent was evaporated under vacuum and the product was collected.

Yield: 10 g.

HPLC Purity: 94.0%

Example-3

Preparation of roflumilast

The product obtained from example-2 (10g) was heated with thionyl chloride (5.8g) and catalytic amount of dimethylformamide (0.5ml) at 80 to 85°C for 1 hour. The solution was concentrated under reduced pressure and the oily residue was dissolved in dry tetrahydrofuran (50 ml).This was added dropwise at 0°C to a suspension prepared from sodium hydride (3.75 g, 60% suspension) and 4-amino-3,5-dichloro pyridine (9.5g) in dry tetrahydrofuran (50 ml) with stirring. The reaction mixture was stirred for 30 minutes and then acidified to pH 2 with hydrochloric acid (1 N). The reaction mixture was extracted with ethylacetate. The extracted solvent was washed with sodium hydrogen carbonate solution (5%) and water followed by concentration under reduced pressure. The residue was dissolved in methanol (45 ml) at 60°C and 5 ml of water was added to get precipitate. The mixture was then cooled to 10°C and filtered to obtain the title product.

Yield: 9.2 g

Purity: 99% (by HPLC)

M.P.: 157-158°C .

WE CLAIM:

1. A process for the preparation of 3-cyclopropylmethoxy-4-difluromethoxy benzoic acid of formula I, as shown in the accompanied drawings, comprising reacting the compound of formula II, as shown in the accompanied drawings, wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl with difluoromethylating agent in the presence of a base followed by desterification of obtained compound of formula III, as shown in the accompanied drawings, wherein R is as defined above, to obtain the compound of formula I.
2. A process for the preparation of 3-cyclopropylmethoxy-4-hydroxy benzoate of formula II, wherein R is as defined above, comprising reacting 3,4-dihydroxy benzoate of formula IV, as shown in the accompanied drawings, wherein R is as defined above, with cyclopropylmethyl derivative of formula V, as shown in the accompanied drawings, wherein X is a leaving group, in the presence of a base.
3. The process according to claim 1 or 2, wherein R represents methyl or ethyl.
4. The process according to claim 1, wherein difluoromethylating agent is selected from the group consisting of difluorochloromethane (freon-22®) and alkyl difluorochloroacetate.
5. The process according to claim 4, wherein alkyl difluorochloroacetate is selected from the group consisting of methyl difluorochloroacetate, ethyl difluorochloroacetate and tertiary butyl difluorochloroacetate.
6. The process according to claim 1 or 2, wherein the base is an organic or inorganic base.
7. The process according to claim 6, wherein organic base is selected from the group consisting of trimethylamine, triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, DBU (1,8-diazabicyclo- [5.4.0]-undec-7-ene), DBN (1,5- diazabicyclo-[4.3.0]-non-5-ene), 4-dimethylamino pyridine and mixtures thereof.
8. The process according to claim 6, wherein inorganic base is selected from the group consisting of alkali metal carbonate, alkali metal bicarbonate and alkali metal hydroxide.
9. The process according to claim 8, wherein alkali metal carbonate is selected from the group consisting of lithium carbonate, sodium carbonate and potassium carbonate.

10. The process according to claim 8, wherein alkali metal bicarbonate is selected from the group consisting of sodium bicarbonate and potassium bicarbonate.
11. The process according to claim 8, wherein alkali metal hydroxide is selected from the group consisting of sodium hydroxide and potassium hydroxide.
12. The process according to claim 1 or 2, wherein the reaction is performed in the presence of a phase transfer catalyst.
13. The process according to claim 12, wherein phase transfer catalyst is selected from the group consisting of quaternary ammonium salts and quaternary phosphonium salts.
14. The process according to claim 13, wherein quaternary ammonium salt is selected from the group consisting of tetramethyl ammonium iodide, tetrabutyl ammonium iodide, benzyltributyl ammonium bromide, 1-methylpyridinium iodide, tetramethyl-2-butylammonium chloride, trimethylcyclopropylammonium chloride, tetrabutylammonium bromide, t-butylethyldimethylammonium bromide and mixtures thereof.
15. The process according to claim 13, wherein quaternary phosphonium salt is selected from the group consisting of tributylmethylphosphonium iodide, triethylmethylphosphonium iodide, methyltriphenoxyphosphonium iodide, tetrabutyl phosphonium bromide, benzyltriphenyl phosphonium bromide, tetraphenyl phosphonium chloride and mixtures thereof.
16. The process according to claim 1 or 2, wherein the reaction is performed in an inert solvent, selected from the group consisting of alkyl ethers, alcohols, ketones, chlorinated hydrocarbons. esters, hydrocarbons, dipolar aprotic solvents, cyclic ethers and mixtures thereof.
17. The process according to claim 16, wherein hydrocarbon is selected from the group consisting of benzene, xylene, toluene, heptane, hexane, cyclohexane, octane and mixtures thereof.
18. The process according to claim 16, wherein dipolar aprotic solvent is selected from the group consisting of dimethylsulfoxide, dimethylformamide and mixtures thereof.
19. The process according to claim 16, wherein cyclic ether is selected from the group consisting of dioxane, tetrahydrofuran and mixtures thereof.
20. The process according to claim 16, wherein ketone is selected from the group consisting of acetone and methyl isobutyl ketone and mixtures thereof.
21. The process according to claim 1, wherein the reaction of compound of formula II with difluoro methylating agent is carried out at temperature range of from about 25°C to about 50°C.

22. The process according to claim 2, wherein leaving group X in the compound of formula V is selected from the group consisting of chlorine, bromine, iodine, sulphate and tosylate.

23. The process according to claim 2, wherein the reaction of compound of formula IV with cyclopropyl methyl compounds is carried out at temperature range of from about 25°C to about 50°C.

24. The process as claimed in claim 1, further comprising conversion of compound of formula I, to roflumilast of formula VI, as shown in the accompanied drawings.

25. The process as claimed in claim 24, wherein the conversion involves reacting an activated derivative of the acid of formula I with 4-amino-3,5-dichloro pyridine.

26. The process as claimed in claim 25, wherein the activated derivative of the acid of formula I is acid halide or a reactive ester of the compound of formula I.

27. The process as claimed in claim 24, wherein the conversion to compound of formula VI is achieved by the reaction of acid chloride of formula I with 4-amino-3,5-dichloro pyridine in the presence of sodium hydride in tetrahydrofuran.

28. A compound of formula II, as shown in the accompanied drawings, wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl.

29. The compound as claimed in claim 28, wherein R is methyl or ethyl.

30. A compound of formula III, as shown in the accompanied drawings, wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl.

31. The compound as claimed in claim 30, wherein R is methyl or ethyl.

32. The process for preparing compound of formula I, as herein described and illustrated by the examples herein.

Dated 12TH day of **September, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

PROCESS FOR THE PREPARATION OF 3-CYCLOPROPYLMETHOXY-4-DIFLUROMETHOXY BENZOIC ACID

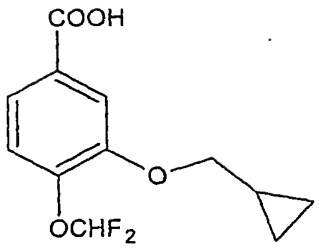
An industrially advantageous process for the preparation of 3-cyclopropylmethoxy-4-difluromethoxy benzoic acid, a key intermediate for the synthesis of roflumilast, is provided.

Ranbaxy Laboratories Limited

Application No.

No. of sheets = 06

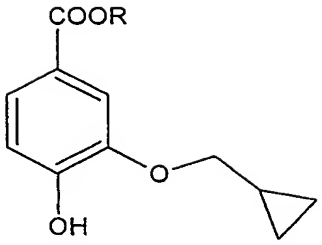
Sheet 01 of 06



formula I

For Ranbaxy Laboratories Limited

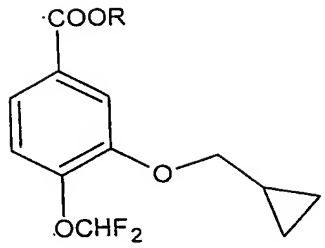
(Sushil Kumar Patawari)
Company Secretary



formula II

For Ranbaxy Laboratories Limited

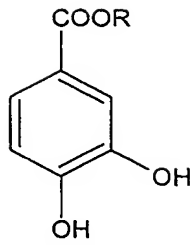
(Sushil Kumar Patawari)
Company Secretary



formula III

For Ranbaxy Laboratories Limited

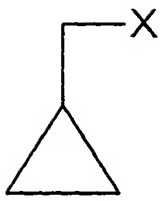
(Sushil Kumar Patawari)
Company Secretary



formula IV

For Ranbaxy Laboratories Limited

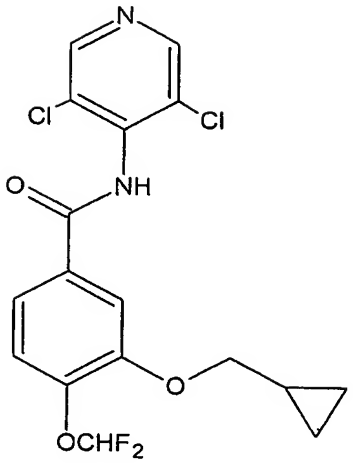
(Sushil Kumar Patawari)
Company Secretary



formula V

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary



Formula VI

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary